Concept Proposal Under the 607 Announcement

Title: Perchlorate exposure and neonatal thyroid hormone levels.

State and Site: Aerojet-General Corporation site, Rancho Cordova, Sacramento County, CA

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Potential Collaborators: California Department of Health Services, Genetic Disease Branch; California Department of Health Services, Environmental Health Investigations Branch

Background:

History of Site: Aerojet began operation in 1951, manufacturing liquid and solid propellants for military and commercial rocket systems. Over the years, Aerojet disposed of hazardous waste by burial, open burning, discharge into unlined ponds and injection into deep underground wells (1). Some of these discharges into the environment moved off-site of the Aerojet facility boundary and contaminated the drinking water supply for residents of the Arden-Cordova water district, near Sacramento, California. The contaminants in the groundwater plume include volatile organic compounds and perchlorate. A recent health consultation performed by the California Department of Health Services' cooperative agreement staff concluded that completed exposure pathways to perchlorate existed and may have posed a health hazard to individuals during the length of time that the affected drinking water wells were in use (2).

Exposures and Outcomes Under Study: The primary exposure of interest is from perchlorate via drinking water contamination. Perchlorate exposure will be estimated by ascertaining past exposures through ground water transport modeling combined with water flow modeling methods for contaminated and uncontaminated drinking water wells to blocks of the affected neighborhoods. Individual residences will be designated into categories of exposure to perchlorate (high, medium, low/no) through this modeling. We are proposing two mechanisms for performing the exposure modeling. The first method will utilize the expertise of individuals in ATSDR's Exposure Investigation and Health Consultation Branch of the Division of Health Assessment and Consultation. These individuals have performed similar investigations at other locations and would be a preferred choice depending on their availability. We have also met with several members of the faculty from the University of California-Davis in the Departments of Land, Air and Water Resources and Civil Engineering who have expressed an interest in this project and have considerable experience in modeling problems of this nature. Assistance from this group (or other interested parties) would be obtained through a bidding process as mandated by ATSDR.

The primary outcome of interest in this study is neonatal thyroid hormone level, as measured by T4 hormone. All live births of individuals in the state have neonatal thyroid hormone blood levels drawn which are recorded by the CDHS's Genetic Disease Branch (GDB). A secondary outcome of interest will be neonatal birth weights, also on file with the GDB. We will attempt to analyze the relationship between maternal perchlorate exposure and neonatal thyroid hormone levels and birth weights for individuals from residences located in the suspected area of perchlorate contamination.

Literature Review: The effects of perchlorate on the thyroid gland have been studied for several decades, but there is still much that is not known about the effects of low-level exposure. It is thought that perchlorate exerts its effects on the thyroid gland by competitively inhibiting the uptake of iodide into the gland, thereby inhibiting the production of thyroid hormones. In response to this inhibition, the pituitary gland increases the release of thyroid-stimulating hormone which stimulates hypertrophy of the thyroid gland (3). The lowest observed adverse effect level (LOAEL) for perchlorate of 1.4 mg/kg/day was found in a study by Stanbury and Wyngaarden of patients with Graves' Disease. No toxic effects of perchlorate were encountered in three patients given no more than three doses of 600 mg. of perchlorate (4). Other suspected adverse effects of perchlorate exposure have been reported to include: skin rash, sore throat, gastrointestinal irritation and lymphadenopathy (5), aplastic anemia (6), and agranulocytosis (7). All of these reactions were observed in patients with Graves' Disease; there is no information which suggests that individuals without this ailment would react in a similar fashion. Other gaps in the literature include: a paucity of information regarding perchlorate's carcinogenic, teratogenic and developmental effects. Specifically, there is limited knowledge as to the effects of maternal ingestion of perchlorate and neonatal hypothyroidism (several animal studies showed increased thyroid weights and size with maternal ingestion of perchlorate, but no hormone levels were obtained [3]) and no studies suggesting that maternal perchlorate ingestion is a risk factor for producing neonatal low birth weight. It is known however, that other goitrogens such as propylthiouracil, lithium and iodides are capable of producing neonatal hypothyroidism by crossing the placenta and inhibiting thyroid hormone synthesis in the neonate (8). It is suspected that perchlorate may act in the same fashion.

Objectives:

1. We will assess whether the consumption of perchlorate-contaminated drinking water by pregnant women leads to demonstrable differences in neonatal thyroid hormone levels between different exposure groups.

2. We will assess whether the consumption of perchlorate-contaminated drinking water by pregnant women leads to demonstrable differences in birth weights of neonates between different exposure groups.

Methods:

Study Design: This study will be a cross-sectional design, with exposure to perchlorate-contaminated drinking water assessed through modeling conducted by the Exposure Investigation and Health Consultation Branch of ATSDR and neonatal thyroid hormone levels and birth weights ascertained from data available electronically through CDHS' Genetic Disease Branch.

Study Population: The study population will consist of all live births which have thyroid hormone blood levels on file with the Genetic Disease Branch. The time period will be from the suspected beginning of exposure (1988?) and continue until exposure was stopped (1997?). This time period is approximate and may be changed as modeling results are completed. The place of residence will be restricted to Rancho Cordova, Sacramento County and will be further restricted to zip code area 95670 (which, at this time, appears to be the most likely zip code area to have been exposed to perchlorate-contaminated water).

Sample Size Estimate:

For an estimated effect size of 1 mIU/dl of T4 and a standard deviation of 4.6 found in a previous observational study of all live birth screenings in Rancho Cordova, the effect/SD= 0.2. With an alpha= 0.05 (two-tailed) and a beta = 0.20, it is estimated that we would need to have approximately 393 individuals in each exposure group (9).

In preliminary research conducted by CDHS, we have ascertained that from 1985-1996 there were 11,773 blood samples tested from neonates born in possible affected zip codes. If only 1/10 of the individuals were from the suspected zip code with the presumed perchlorate exposure, we would still have approximately 1200 individuals available for this study, which would be approximately enough to detect statistical significance if the individuals were evenly divided. We presume that there would be more than this number of individuals available for analysis.

Data Collection: Exposure will be ascertained by drinking water modeling using hydrolic flow and water pressure information from the water purveyor (Arden-Cordova Water Service) and hydrogeology information from Aerojet. Based on prior dose-reconstruction analyses performed by ATSDR in other locations, we believe that estimates of doses can be obtained to the census block level for specific time periods. We have received permission from the Committee for the Protection of Human Subjects of the California Department of Health Services (see attached letter of approval) to obtain thyroid hormone levels and neonatal birth weights from computer files maintained by the GDB along with the residence of the neonate at the time of birth (address, city, state and zip code). We will also abstract the race, and sex of the newborn as well as the mother's birthdate from records on file at the GDB because these factors may be confounders for the relationship between the exposure of interest and neonatal thyroid levels. Confounders which we will be able to control for related to maternal perchlorate ingestion during pregnancy and low birth weight include: maternal age (maternal birthdate), race and sex of the newborn (from GDB data).

Data Analysis: The data will be initially analyzed to determine its character (normality or non-normality). Should the data be determined to be normally distributed, then ANOVA techniques will be required to test the differences of group means with maternal exposure to perchlorate (independent variable) characterized in three groups (high, medium and low/no) and neonatal thyroid hormone level (T4) as the dependent variable. Should the data be non-normally distributed, then non-parametric analysis using the Kruskall-Wallis statistical test will be conducted. The median hormone level observed for each exposure group will be tested with the null hypothesis that there are no differences between the groups. Should any of the means or medians differ, further exploration of these differences will be performed by Tukey analysis. This process will also be repeated for the analysis of neonatal birth weights, the secondary outcome of interest. Confounders for perchlorate ingestion and both neonatal thyroid hormone levels and low birth weight will be addressed by adjusting for the confounders (which have been mentioned above) in the analyses.

To further assess whether perchlorate ingestion is a risk factor for neonatal hypothyroidism, we obtained the statewide data for neonatal thyroid hormone levels (based on almost 6.5 million screenings from 1985 through 1996) and calculated the T4 level for the lowest 5% of that population (8.2 mIU/dl). This figure will be used as the cut-point for the study area's population, with individuals being placed in one of two groups based on whether they fall above (controls) or below (cases) the cut-point. Our cut-point is approximately 1 mIU/dl lower than a more recent (1997) GDB screening cut-point for hypothyroidism and published laboratory values for T4 levels in newborns, but should be more sensitive in finding actual clinical cases of neonatal hypothyroidism. It is however, unclear whether any of these levels translate into finding more actual clinical cases of neonatal hypothyroidism, as during this same time period only 4 cases of clinical hypothyroidism were observed out of 11,773 screenings (0.03%).

The groups will then be further classified by maternal exposure to perchlorate-contaminated drinking water (yes vs. no). Logistic regression of this data will then be performed to determine if maternal perchlorate ingestion is a risk factor for the development of low levels of thyroid hormone in neonates.

Should we determine that there are statistically significant differences in the means or medians of each group's thyroid hormone level and birth weight or if it is observed that maternal perchlorate ingestion is a significant risk factor for hypothyroidism in neonates, further study will be required. The next phase of this study will require obtaining further permission from the Committee for the Protection of Human Subjects to conduct questionnaire interviews of mothers who resided in the affected area regarding the duration and intensity of their exposure and any confounding factors which may have contributed to the effects observed. The actual design of the questionnaire and a formal proposal for this phase of the study is pending completion of the initial part of the investigation and will be submitted separately to ATSDR, if needed.

Strengths and Limitations: The strength of this study will be its utilization of modeling data to more accurately assess the exposure of pregnant women to perchlorate-contaminated drinking water. In addition, because we are using continuous values of thyroid hormone level and birth weights, we have increased power in this study and may be able to detect smaller amounts of effect with different levels of thyroid hormone.

The limitations of this study are related to the ground water modeling assessments. The exposure dose is an assumed exposure and may not reflect the actual water intake during the pregnancy. There also may be other confounders which are related to drinking water consumption and the outcome of interest, neonatal thyroid hormone levels which are not accounted for in this study and will possibly need to be answered by a questionnaire from a sample of potentially-exposed participants.

Approximate Budget with Funding Sources:

see attached spreadsheet

References

1. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. Health Consultation for Aerojet-General Corporation. February 21, 1997, p. 1.

2. Environmental Health Investigations Branch, California Department of Health Services. Health Consultation: Perchlorate Contamination in the Arden-Cordova Water Service Area. Prepared for the U.S. Agency for Toxic Substances and Disease Registry. September 29, 1997.

3. Toxicology Excellence for Risk Assessment. Proposed Perchlorate Reference Dose (RfD). February, 1997, p.5.

4. Stanbury JB and Wyngaarden JB. Effect of perchlorate on the human thyroid gland. Metabolism 1952; 1: 533.

5. Morgans ME and Trotter WR. Potassium perchlorate in thyrotoxicosis. British Journal of Medicine 1960; 1086.

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8. DiGeorge A. "Disorders of the thyroid gland" in Nelson: Textbook of Pediatrics. Behrman RE and Vaughan VC (eds.). Philadelphia: W.B. Saunders Company, 1983.

9. Designing Clinical Research. Hulley SB and Cummings SR (eds.). Baltimore: Williams and Wilkins, 1988.